EXHIBIT K

UROGYNECOLOGY

One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse

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OBJECTIVE: The purpose of this study was to show 12-month outcomes of a randomized trial that compared vaginal prolapse repair with and without mesh.

STUDY DESIGN: Women with stage ≥2 prolapse were assigned randomly to vaginal repair with or without mesh. The primary outcome was prolapse stage ≤1 at 12 months. Secondary outcomes included quality of life and complications.

RESULTS: All 65 evaluable participants were followed for 12 months after trial stoppage for mesh exposures. Thirty-two women had mesh repair; 33 women had traditional repair. At 12 months, both groups had improvement of pelvic organ prolapse-quantification test points to similar recurrence rates. The quality of life improved and did not differ between groups: 96.2% mesh vs 90.9% no-mesh subjects reported a cure of bulge symptoms; 15.6% had mesh exposures, and reoperation rates were higher with mesh.

CONCLUSION: Objective and subjective improvement is seen after vaginal prolapse repair with or without mesh. However, mesh resulted in a higher reoperation rate and did not improve 1-year cure.

Key words: exposure, prolapse repair, randomized trial, vaginal mesh

Cite this article as: Sokol AI, Iglesia CB, Kudish BI, et al. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012;206:86.e1-9.

The use of mesh to augment vaginal prolapse repairs has become a topic of considerable debate over the past few years. Proponents of mesh use point to the up to 30% reoperation rate quoted in some studies for traditional vaginal prolapse repair surgeries.[1] Initial retrospective and prospective cohort studies showed high success rates with few complications.[2-7] A few published studies have shown some benefit of synthetic mesh-augmented procedures over traditional repairs for the anterior compartment.[8,9] However, the rise in mesh augmentation led to increased reports of mesh-related complications, which prompted a Food and Drug Administration advisory about the use of mesh in pelvic surgery.[10] Given the rise in litigation surrounding mesh repairs, particularly after the Food and Drug Administration advisory, some investigators recently have suggested that separate consent forms be used for prolapse repair that involves mesh.[11] This makes the analysis of the potential risks and benefits of mesh for vaginal prolapse repair more important than ever.

Currently, no double-blind randomized controlled trials (RCTs) have evaluated the long-term effectiveness of these procedures for multicompartment prolapse. The primary objective of this double-blind, multicenter RCT was to test the hypothesis that the addition interpositional polypropylene mesh improves the 1-year objective treatment success (pelvic organ prolapse–quantification [POP-Q] stage ≤1) of vaginal reconstructive surgery for pelvic organ prolapse compared with traditional vaginal reconstructive surgery without mesh. Secondary objectives were to compare patient satisfaction, quality-of-life (QOL) variables, short-term and long-term complications, vaginal caliber and morbidity that were related to mesh use between the 2 arms of the trial.

Materials and Methods

This multicenter, double-blind RCT was conducted by 6 fellowship-trained pelvic reconstructive surgeons at Washington Hospital Center, Stanford University and Yale University. Institutional review board approval was obtained at each site, and all

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Received April 21, 2011; revised July 6, 2011; accepted Aug. 4, 2011.

Supported by a grant from the American Urogynecologic Society Foundation and a MedStar Health Research Institute Intramural Grant.

R.B. has received payment from Gynecare for lectures, consulting, and proctoring surgical cases within the last 3 years. The other authors report no conflict of interest. Prolift mesh kits for this study were donated by Ethicon Women's Health and Urology, Somerville, NJ.

Presented orally at the 31st annual meeting of the American Urogynecologic Society, Long Beach, CA, Sept. 30-Oct. 2, 2010.

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women provided written informed consent to participate. A detailed description of the study methods and trial design has been published previously.[12] Briefly, women with POP-Q prolapse stages 2-4 were assigned randomly to traditional vaginal prolapse repair without mesh (primarily combined anterior/posterior colporrhaphy and uterosacral ligament suspension) or vaginal colpopexy with mesh (Prolift; Ethicon Women's Health and Urology, Somerville, NJ). Random assignment occurred with computer-generated random numbers that were stratified for presence or absence of a uterus. Opaque sealed envelopes were opened in the operating room after the patient received anesthesia. The research study nurse coordinator at each site, other research staff, and the patient were masked to the treatment assignment. The primary outcome measure was objective treatment success (POP-Q stage ≤1) at 12 months. Secondary outcome measures included QOL variables, lower urinary tract function, vaginal caliber, and complication rates. Stopping criteria were set with the use of a .001 level of significance and a >15% observed mesh exposure rate, >1% mesh infection rate, >1% fistula formation, and >5% rate of de novo dyspareunia.

Surgery

The surgical techniques in both the mesh and no-mesh groups have been described previously.[12] The techniques for the procedures were standardized for uniformity and included choice of sutures for uterosacral ligament suspension or sacrospinous fixation (combination delayed absorbable polydioxanone sutures [Ethicon, Somerville, NJ]) and permanent polytetrafluoroethylene sutures (Gore-tex; W.L. Gore & Associates, Flagstaff, AZ) and a choice of vaginal mesh kit (Prolift). Apical suspension with uterosacral ligament suspension or sacrospinous suspension (no-mesh arm) vs total vaginal mesh (total Prolift) or modification (anterior Prolift with the insertion of the posterior arms through the sacrospinous ligament; mesh arm) was performed if the cuff or posterior fornix was <3 cm proximal to hymeneal remnant (point C and D ≥ –3) or if the surgeon believed there to be the need for additional apical support. The uterosacral ligament suspension was conducted as described by Shull et al[13]; the Prolift procedures were performed in accordance with product recommendations. To maintain patient masking, steristrips were placed on the vulva after the surgery (to mimic dressings placed after Prolift), regardless of treatment assignment.

All surgeons were fellowship trained and had performed >30 vaginal colpopexy procedures with uterosacral and sacrospinous ligaments and a minimum of 10 Prolift procedures before patients were enrolled in the trial.

Outcome measures

The primary outcome measure for objective treatment success was overall POP-Q stage ≤1 (descent at >1 cm proximal to the hymen) at 1 year. The need for additional surgical treatment or pessary placement for recurrent prolapse at any time after the initial procedure also constituted treatment failure. These definitions conform to the recommendations from the National Institutes of Health Terminology Workshop for Researchers in Female Pelvic Floor Disorders.[14]

The secondary outcome measures for objective treatment success consisted of anterior, apical, and posterior prolapse stage ≤1 (Ba, Bp, and C >1 cm proximal to the hymen) at 1 year. POP-Q measurements were obtained at 3 and 12 months and yearly thereafter by blinded examiners who had been trained in the performance of POP-Q. For the secondary outcomes, each compartment was analyzed separately for cure. Socioeconomic characteristics, risk factors, and preoperative prolapse severity were investigated as possible factors that could influence the outcome in each arm. Impact on QOL was assessed with validated questionnaires. Preoperative QOL questionnaires were completed at enrollment, at 3 and 12 months, and yearly thereafter. A research nurse coordinator updated contact information, medical history, and adverse events during a 6-month postoperative telephone interview. The following validated QOL tools were used: the SF-12[15] with both Physical Component Summary and Mental Component Summary, the short forms of Pelvic Floor Distress Inventory that included subscales of Pelvic Organ Prolapse Distress Inventory, the Colorectal Anal Distress Inventory, the Urogenital Distress Inventory, the Pelvic Floor Impact Questionnaire with the corresponding Colorectal Anal Impact Questionnaire, the Pelvic Organ Prolapse Impact Questionnaire and the Urinary Impact Questionnaire,[16] the Prolapse and Incontinence Sexual Questionnaire,[17] the Patient Global Impression of Improvement,[18] and the Patient Global Impression of Severity.[18]

Perioperative measures of morbidity that included operative time, estimated blood loss, and intra- and postoperative complications were recorded at the completion of surgery, at hospital discharge, and at the 6-week postoperative visit. Complications were categorized with a modification of the Dindo Classification.[19]

Women who completed at least approximately 1 year of follow-up evaluation were compared with respect to changes in vaginal caliber that was measured by a ring pessary (diameter in centimeters) at baseline, at 3 and 12 months, and yearly thereafter; to vaginal volume (formula: volume of a cylinder πr^2total vaginal length; cubed centimeters), and POP-Q measurements. One-year Prolapse and Incontinence Sexual Questionnaire-12 scores and dyspareunia for sexually active women were compared with baseline.

Statistical methods

Methods of data analysis and sample size calculation have been described previously.[12] SPSS software for Windows (version 16; SPSS Inc, Chicago, IL) was used for data management and statistical analysis. A .05 significance level was used for all statistical tests. No 1-sided tests were done. For vaginal caliber and sexual function, Mann-Whitney, χ^2, Fisher's exact, and Spearman correlation tests were used for statistical analysis. Survival analysis methods were used to analyze times to recurrence, because these variables had censored data. The log-rank test and Cox proportional hazards regression were used to compare independent groups with respect to recurrence and exposure. Means are presented as mean ± standard deviation or mean (range). Me-

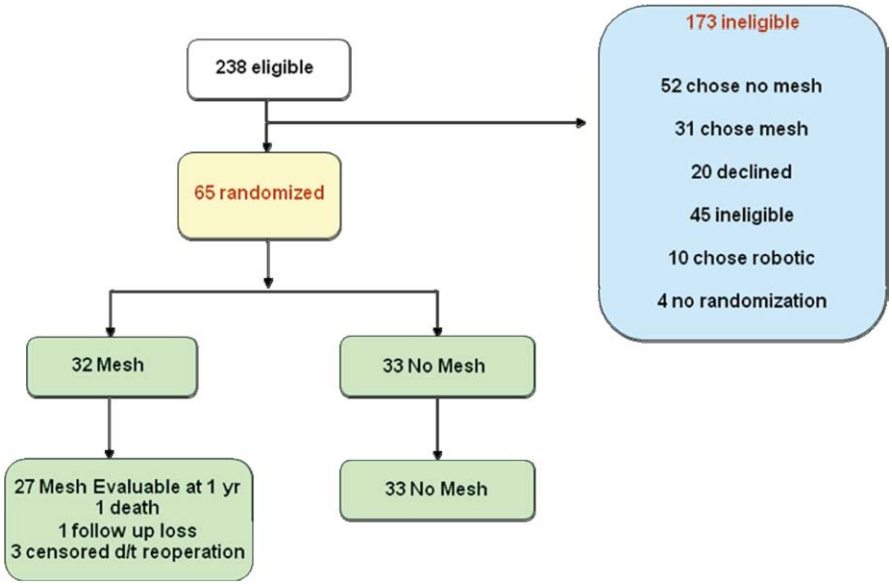
dians are presented as median (range). Data that were obtained after repeat surgery for prolapse recurrence were not included in the analyses, which was done to eliminate the chance that data would be skewed toward improved outcomes after repeat surgery.

RESULTS

Recruitment began on January 3, 2007, and continued until August 1, 2009, at which time the study was halted because of predetermined criteria for vaginal mesh exposure at a mean follow-up time of 7.2 months (range, 2.1–14.7 months). Recruited patients were then observed until all evaluable participants (60/65; 92.3%) reached ≥12 months of follow up (mean, 14.7 months) with a POP-Q evaluation. Enrollment and disposition of the trial are summarized in the Figure. The conditions of 5 patients in the mesh arm were not evaluable at 12 months and were thus censored from the analysis: 1 patient died of a myocardial infarction after 3.7 months; 1 patient did not return for follow-up evaluation after 7.2 months, and 3 patients needed additional prolapse surgery at <12 months of follow up (4.6, 9.8, and 10.2 months). All patients in the no-mesh arm were evaluated at 12 months. Thirty-two subjects (49.2%) had mesh surgery; 14 of these subjects (44%) had undergone hysterectomy earlier. Thirty-three subjects (50.8%) had no-mesh surgery; 12 of these subjects (36%) had undergone hysterectomy earlier. Baseline characteristics did not differ significantly between these 2 groups (Table 1). With the exception of posterior repair that was performed more commonly in the no-mesh group (56% vs 82%; $P = .026$), similar procedures were performed concomitantly in each group.[12] Operative times were similar between the mesh (3.0 ± 0.8 hours) and no-mesh groups (3.1 ± 1.0 hours; $P = .53$). Estimated blood loss was also similar (mesh group, 124.5 ± 79.7 mL vs no-mesh group, 154.5 ± 107.1 mL; $P = .29$).

There was a statistically significant difference between the mesh and no-mesh groups with respect to months of follow up: the mesh group had a mean time of 13.2 ± 4.7 months and a median time of 12.2 months (range, 3.7–26.7 months); the no-mesh group had a mean time of 16.2 ± 5.4 months and a median time of 13.1 months (range, 11.6–27.7 months; $P = .037$). There were no statistically significant differences between the mesh and no-mesh groups with respect to the preoperative overall POP-Q stage or the preoperative POP-Q stage by points Ba, Bp, or C (Mann-Whitney test, $P = .31$ to .63). At approximately 12 months after the procedure, both groups had statistically significant improvements of POP-Q points C, Ba, and Bp ($P < .001$; $P = .002$).

FIGURE
The passage of participants through the randomized trial



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Objective recurrence

No statistically significant differences in overall recurrence (postoperative overall POP-Q stage ≥2; $P = .45$) or in recurrence by compartment were found between the mesh and no-mesh groups (Table 2). A total of 43 subjects (66.2%) had an objective recurrence of stage ≥2 prolapse in 20 of the mesh subjects (62.5%) compared with 23 of the no-mesh subjects (69.7%). Of the 43 recurrences, 33 recurrences (76.7%) were at or proximal to the hymeneal remnant: 15 of the mesh group (75.0%) vs 18 of the no-mesh group (78.3%; $P > .99$). Ten of the 43 recurrences (23.3%) were distal to the hymeneal remnant. Most recurrences involved the anterior compartment (15 mesh and 19 no-mesh subjects).

No statistically significant differences were found between the mesh and no-mesh groups with respect to anterior wall recurrence (postoperative POP-Q stage ≥2 at point Ba; $P = .30$) or posterior wall recurrence (postoperative POP-Q stage ≥2 at point Bp; $P = .66$). Fifteen of the mesh subjects (46.9%) vs 20 of the no-mesh subjects (60.6%) had an anterior wall recurrence ($P = .40$), and 7 subjects (21.9%) vs 6 subjects (18.2%) had a posterior wall recurrence ($P = .61$), respectively. Three months after the operation, the point Ba measurement was significantly better for the mesh group, even though overall anterior POP-Q stage recurrence was not significantly different.[11] At 12 months, however, the difference in point Ba was no longer statistically significant ($P = .077$). Only 1 subject had an apical recurrence (postoperative POP-Q point C at stage ≥2). This patient had a redundant 14-cm vagina, and the surgeon made the clinical decision to trim the excess epithelium and muscularis. Because of the

TABLE 1
Baseline characteristics of study participants

Characteristic	Group Mesh	No mesh	*P* value
Age, y[a]	64.4 ± 10.8	63.5 ± 8.9	.61
Race, n (%)			.70[b]
White	20 (62.5)	22 (66.7)	
African American	8 (25.0)	7 (21.2)	
Hispanic	3 (9.4)	3 (9.1)	
Asian	1 (3.1)	0	
Other	0	1 (3.0)	0
Postmenopausal, n (%)	30 (93.8)	31 (93.9)	1
Married, n (%)	20 (62.5)	21 (63.6)	.92
Educational level, n (%)			.40
<High school	0	2 (6.1)	
Completed high school	10 (31.3)	11 (33.3)	
College or graduate	22 (68.8)	20 (60.6)	0
Health insurance, n (%)			.54
Private	15 (46.9)	18 (54.5)	
Medicare	17 (53.1)	15 (45.5)	
Current smoker, n (%)	4 (12.5)	2 (6.1)	.43
Parity n	2.4 ± 1.1	2.6 ± 0.9	.30
Previous vaginal deliveries, n	2.3 ± 1.2	2.5 ± 0.8	.28
Hysterectomy, n (%)	14 (43.8)	12 (36.4)	.54
Previous surgery for prolapse, n (%)	4 (12.5)	0	.053
Previous surgery for incontinence, n (%)	2 (6.3)	1 (3.0)	.61
Body mass index, kg/m^2	27.4 ± 5.1	27.8 ± 6.4	.71
Body mass index ≥30 kg/m^2, n (%)	8 (25.0)	9 (27.3)	.84
Pelvic organ prolapse–quantification stage, n (%)			.51
II	7 (21.9)	4 (12.1)	
III	20 (62.5)	24 (72.7)	
IV	5 (15.6)	5 (15.2)	
Pelvic organ prolapse–quantification measurements, cm[c]			
Ba	3.0 (0.0–13.5)	4.0 (−0.5 to 9.0)	.29
Bp	−1.0 (−3.0 to 13.5)	−1.0 (−3.0 to 8.0)	.75
C	−0.8 (−7.5 to13.5)	2.0 (−8.0 to 9.0)	.26
GH	5.0 (2.0–8.0)	5.0 (2.5–8.0)	.27
PB	4.0 (2.0–5.0)	3.5 (1.0–5.5)	.15
Total vaginal length	9.0 (6.5–13.5)	9.0 (7.0–11.5)	.50

The χ^2 test of association was used to compare the groups with respect to percentages; the Mann-Whitney test was used to compare the groups with respect to noncategoric variables.

[a] Data are given as mean ± SD; [b] Based on white and African American groups only; [c] Data are given as median (range).

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need to trim the excess vagina, the surgeon divided the mesh potentially to decrease the risk of exposure at the apex. This woman was in the hysterectomy group and had a postoperative stage 4 prolapse at point C at 2.1 months after a total Prolift. A summary of overall objective anatomic outcomes and global impressions of improvement and severity at a mean follow-up time of 14.3 months (Table 2).

In the mesh group, there was no association between the site of mesh placement and the site of recurrence (Table 3). For patients with recurrences, no statistically significant differences were found between the mesh and no-mesh groups with respect to the percentages with anterior, posterior, or apical recurrences ($P = .44$-$.53$). Three patients in the mesh group had reoperations for prolapse (2 sacral colpopexies and 1 iliococcygeal suspension) vs no reoperations in the no-mesh group ($P = .11$).

Patient satisfaction and QOL

The mesh group had significantly lower overall preoperative distress that was indicated by lower preoperative Pelvic Organ Prolapse Distress Inventory -6 scores than the no-mesh group (Table 4). Postoperative subjective QOL measurements showed statistically significant improvements from baseline for both the mesh and no-mesh groups for almost all QOL measurements and did not differ between the 2 groups 1 year after the procedure (Table 4). Patients in both groups had high subjective satisfaction at 1 year after the procedure, with no statistically significant difference between the mesh and no-mesh groups ($P = .44$). Subjective cure of bulge symptoms was reported by 25 of mesh subjects (96.2)% and 30 of no-mesh subjects (90.9%) at 12 months ($P = .62$).

Colorectal function

Colorectal function that was based on Colorectal Anal Distress Inventory–8 and Colorectal Anal Impact Questionnaire–7 scores was similar before the procedure between the mesh and no-mesh groups and improved significantly in both groups 12 months after the procedure. No significant difference was found between groups with regards to

colorectal function 12 months after the procedure (Table 4).

Sexual function

Sexual function based on the Prolapse and Incontinence Sexual Questionnaire scores was similar before the procedure between mesh and no-mesh groups and improved significantly in both groups 12 months after the procedure. No significant difference was found between groups with regards to sexual function 12 months after the procedure (Table 4).

Vaginal caliber

Preoperative vaginal diameter (median, 7.6 cm [range, 5.7–8.9 cm] vs 7.6 cm [range, 6.4–8.9 cm]; $P = .15$) and vaginal volume (median, 384.8 cm^3 [range, 204.1–684.3 cm^3] vs 408.3 cm^3 [range, 257.4–622.2 cm^3]; $P = .26$) were similar between the mesh and no-mesh groups. Patients with previous hysterectomy had significantly lower preoperative vaginal diameter (median, 7.3 cm [range, 5.7–8.9 cm] vs 7.6 cm [range, 6.4–8.9 cm]; $P = .027$) and volume (median, 346.4 cm^3 [range, 204.1–612.4 cm^3] vs 408.3 cm^3 [range, 257.4–684.3 cm]; $P = .005$) than did those without previous hysterectomy. At 1 year, both the mesh and no-mesh groups had statistically significant decreases in postoperative vaginal diameter (mesh group: median, 7.6 cm [range, 5.7–8.9 cm] vs 6.1 cm [range, 5.7–7.0 cm]; $P < .001$; no-mesh group: median, 7.6 cm [range, 6.4–8.9 cm] vs 6.4 cm [range, 5.17.0 cm]; $P < .001$), vaginal volume (mesh group: 384.8 cm^3 [range, 204.1–684.3 cm^3] vs 214.7 cm^3 [range, 153.1–321.7 cm^3]; $P < .001$; no-mesh group: 408.3 cm^3 [range, 257.4–622.2 cm^3] vs 257.4 cm^3 [range, 127.6–384.8 cm^3]; $P < .001$), and total vaginal length (mesh group: median, 9.0 cm [range, 6.5–11.0 cm] vs 8.0 cm [range, 6.0–10.0 cm]; $P < .001$; no-mesh group: median, 9.0 cm [range, 7.0–11.5 cm] vs 8.0 cm [range, 5.0–10.0 cm]; $P < .001$) compared with preoperative values, but no statistically significant differences were found between the mesh and no-mesh groups ($P = .25$-$.40$).

Complications

Two cystotomies occurred in the mesh group, 1 during dissection and 1 during trocar insertion. Both subjects with cystotomies had previous hysterectomies; the cystotomies were repaired, and mesh was placed without complication or subsequent postoperative sequelae. No serious adverse events that were related to surgery occurred in either group. One subject in each group had a febrile illness while hospitalized. One subject in the mesh group with concurrent hysterectomy received a postoperative blood transfusion. No significant differences

TABLE 2
Anatomic outcomes and quality of life evaluation 12 months after surgery

Variable	Mesh	No mesh	*P* value
National Institutes of Health optimal prolapse by POP-Q stage ≤1: mesh, 32; no mesh, 33, n (%)	12 (37.5)	10 (30.3)	.45
Prolapse by symptoms (bulge): mesh, 26; no mesh, 33, n (%)[a,b]	1 (3.8)	3 (9.1)	.62
Recurrent prolapse: mesh, 20; no mesh, 23, n (%)			> .99
At or above hymen	15 (75.0)	18 (78.3)	
Beyond hymen	5 (25.0)	5 (21.7)	
Reoperation for prolapse: mesh, 32; no mesh, 33, n (%)	3 (9.4)	0	.11
Total reoperation for prolapse or mesh erosion: mesh, 32; no mesh, 33, n (%)	5 (15.6)	0	.017
Point Ba value after operation, cm[b,c]	–1.5 (–3.0 to 0.5)	–1.0 (–3.0 to 1.0)	.077
Point Bp value after operation, cm[b,c]	–2.5 (–3.0 to 0.0)	–3.0 (–3.0 to 0.0)	.27
Point C value after operation, cm[b,c]	–6.0 (–9.0 to –4.5)	–6.5 (–9.0 to –5.0)	.088
TVL: mesh, 27; no mesh, 33[b,c] (mesh, 27; no mesh, 33)	8.0 (6.0–10.0)	8.0 (5.0–10.0)	.35
Patient global impression of improvement: mesh, 26; no mesh, n (%)[b]			0.44
Very much better	16 (61.5)	23 (69.7)	
Much better	6 (23.1)	8 (24.2)	
A little better	0	0	
No change	2 (7.7)	0	
A little worse	1 (3.8)	1 (3.0)	
Much worse	1 (3.8)	0	
Very much worse	0	1 (3.0)	
Patient global impression of severity: mesh, 26; no mesh, 33, n (%)[b]			.71
Normal	18 (69.2)	24 (72.7)	
Mild	6 (23.1)	8 (24.2)	
Moderate	1 (3.8)	0	
Severe	1 (3.8)	1 (3.0)	

The χ^2 test of association was used to compare the groups with respect to percentages; the Mann-Whitney test was used to compare the groups with respect to non-categorical variables.
TVL, total vaginal length.

[a] Bulging sensation present by Pelvic Floor Distress Inventory, item 3; [b] Patients who underwent reoperation for prolapse were excluded from analysis; [c] Data are given as median (range).

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TABLE 3
Mesh placement site vs recurrence site (n = 20)

	Recurrence site, n (%)			
Placement site	Anterior only	Posterior only	Anterior and posterior	Anterior, posterior, and apical
Anterior only	9 (64.3)	4 (28.6)	1 (7.1)	0
Anterior and posterior (total)	4 (66.7)	1 (16.7)	0	1 (16.7)

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were found between the mesh and no-mesh groups with respect to estimated blood loss, preoperative or postoperative hematocrit level, hospital length of stay (Mann-Whitney test, $P = .082$ to 1.0), or 2-week urinary tract infection rate (Fisher's exact test, $P = .20$ to .59). One patient experienced fluctuance and induration at a mesh trocar site 11.5 weeks after anterior Prolift. Incision and drainage were performed in the office, and the patient was treated with Augmentin for 10 days with complete symptom resolution. Abscess cultures were negative.

Of the 32 mesh subjects, 5 women (15.6%) had mesh exposures. One exposure occurred in the concurrent hysterectomy group, and 4 exposures occurred in the previous hysterectomy/vault prolapse group; however, this did not reach statistical significance (log-rank test, $P = .080$). Exposures occurred at 2 weeks, 6 weeks (2 subjects), 7.5 weeks, and 2.1 months and were located along incision lines in the anterior compartment in 3 cases and posterior compartment in 2 cases. Exposures were noted only with Prolift mesh and not with sling mesh. Three of the 5 exposures required additional procedures in the operating room to remove the mesh (Table 5). All exposures resolved after outpatient trimming, without further exposures in these patients. Two exposures were found at the 6-week postoperative visit; 1 of these exposures was trimmed in the office, and the other was asymptomatic and not treated. Both exposures persisted but were asymptomatic at the 1-year visit. During the second interim analysis (when two-thirds of patients reached the 3-month mark), the Data Safety Monitoring Board notified the investigators that the mesh exposure rate had surpassed the predetermined stopping criteria of 15%, and further enrollment in the trial was halted.

Of the 33 no-mesh participants, 5 women (15%) had apical Gore-tex suture exposures; 2 women complained of vaginal discharge and required suture removal in the office at 6 and 9 months after the procedure. One asymptomatic suture Gore-tex suture exposure was noted at 6 months, and another was noted at 12 months; neither exposures required intervention. Another participant had a mild pink discharge and was found to have suture exposure at 16.5 months. However, she was not bothered and chose not to have the suture removed.

No statistically significant differences were found between the mesh and no-mesh groups with respect to long-term complications. De novo stress urinary incontinence developed in 4 of 13 women (30.8%) in the mesh group vs 3 of 19 women (15.8%) in the no-mesh group ($P = .40$). One patient in the mesh group underwent a sling procedure for stress urinary incontinence after the initial prolapse repair (Table 5). No statistically significant differences were found between the mesh and no-mesh groups with respect to new-onset dyspareunia (mesh group, 1/11 women [9.1%] vs no-mesh group, 3/14 women [21.4%]; $P = .60$). The number of participants whose condition required reoperation for recurrent prolapse or mesh exposure was significantly higher in the mesh group: 5 women (15.6%; 3 reoperations for prolapse, 3 reoperations for exposure, with 1 patient having surgery for both prolapse and exposure) vs none in the no-mesh group ($P = .017$). Table 5 details reoperations for exposures and prolapse recurrence.

Two patients died of causes that were unrelated to prolapse repair during the study period. One participant in the mesh group died of myocardial infarction 12 months after surgery (but before her 12-month follow-up visit) and was censored from the 1-year analysis. Another participant in the no-mesh group died 15 months after the procedure after experiencing complications that were related to a diverticular abscess with sepsis.

COMMENT

The key finding of our study was that significant objective and subjective improvements were seen after prolapse repair with or without interpositional mesh. However, mesh was associated with a higher overall reoperation rate and resulted in a >15% risk of exposure.

Strengths and weaknesses of this study have been reported previously.[12] The major strength of this trial is its double-blind, multicenter RCT design. Although mesh kits were provided by the company to maintain patient masking, this study was not industry funded and had excellent follow-up evaluation. Findings of this study should be generalizable to other fellowship-trained pelvic reconstructive surgeons.

The major weakness of this trial was a lack of statistical power for efficacy outcomes because of premature stopping as a result of reaching predetermined mesh exposure rates of >15%. Additionally, some of the complication outcomes may have been "inevitable" because complications resulted in termination of the study. Another potential weakness is the differential follow up between groups. A shorter follow-up period did give the mesh group a slight advantage, because women in this group had less time to have recurrences. Finally, the relatively small number of patients who were available and who consented to participate could call into question the surgical experience of the investigators with mesh. However, our trial was conducted by fellowship-trained surgeons with expertise in all routes of reconstructive pelvic surgery that represent the skilled surgeons to whom new technology often is marketed. All surgeons are in high volume institutions with American Board of Obstetrics and Gynecology/American

TABLE 4
Health-related quality of life variables[a]

Variable	Before the operation		12 mo after the operation		*P* value		12 mo after the operation
	Mesh	No mesh	Mesh	No mesh	Within groups: Mesh	Within groups: No mesh	Between groups: Before the operation
Pelvic Floor Distress Inventory–20[b]	100.0 (0, 235.4) (n = 32)	140.6 (16.7, 284.4) (n = 33)	29.6 (0, 97.9) (n = 26)	29.2 (0, 255.2) (n = 33)	< .001 (n = 26)	< .001 (n = 33)	.084 (n = 65)	.66 (n = 59)
Pelvic Organ Prolapse Distress Inventory–6	43.8 (0, 91.7) (n = 32)	58.3 (16.7, 100) (n = 33)	0.0 (0, 29.2) (n = 26)	0 (0, 75.0) (n = 33)	< .001 (n = 26)	< .001 (n = 33)	.021 (n = 65)	.79 (n = 59)
Colorectal Anal Distress Inventory–8	14.1 (0, 75.0) (n = 32)	34.4 (0, 84.4) (n = 33)	10.4 (0, 56.3) (n = 26)	12.5 (0, 96.9) (n = 33)	.074 (n = 26)	.028 (n = 33)	.15 (n = 65)	.64 (n = 59)
Urogenital Distress Inventory–6	37.5 (0, 100) (n = 32)	45.8 (0, 100) (n = 33)	8.3 (0, 50.0) (n = 26)	12.5 (0, 83.3) (n = 33)	.002 (n = 26)	< .001 (n = 33)	.58 (n = 65)	.71 (n = 59)
Pelvic Floor Impact Questionnaire–7[b]	23.8 (0, 285.7) (n = 32)	38.1 (0, 233.3) (n = 32)	2.4 (0, 90.5) (n = 26)	0 (0, 157.1) (n = 33)	.002 (n = 26)	< .001 (n = 32)	.81 (n = 64)	.70 (n = 59)
Pelvic Organ Prolapse Impact Questionnaire–7	2.4 (0, 95.2) (n = 32)	9.5 (0, 100) (n = 32)	0.0 (0, 9.7) (n = 26)	0 (0, 19.1) (n = 33)	.021 (n = 26)	< .001 (n = 32)	.48 (n = 64)	.10 (n = 59)
Colorectal Anal Impact Questionnaire–7	4.8 (0, 95.2) (n = 32)	4.8 (0, 85.7) (n = 33)	0.0 (0, 23.7) (n = 26)	0 (0, 66.7) (n = 33)	.008 (n = 26)	.039 (n = 33)	.89 (n = 65)	.97 (n = 59)
Urinary Impact Questionnaire–7	14.3 (0, 100) (n = 32)	19.0 (0, 100) (n = 33)	0.0 (0, 90.5) (n = 26)	0 (0, 85.7) (n = 33)	.007 (n = 26)	< .001 (n = 33)	.98 (n = 65)	.53 (n = 59)
Prolapse and Incontinence Sexual Questionnaire–12[c]	31.0 (19.0, 43.6) (n = 17)	32.0 (16.0, 42.0) (n = 17)	34.0 (27.0, 43.0) (n = 15)	35.0 (29.0, 45.0) (n = 16)	.007 (n = 13)	.002 (n = 16)	> .99 (n = 34)	.66 (n = 31)
Dyspareunia, n (%)[d]	3 (17.6) (n = 17)	3 (16.7) (n = 18)	1 (6.7) (n = 15)	3 (18.8) (n = 16)	> .99 (n = 13)	> .99 (n = 16)	> .99 (n = 35)	.60 (n = 31)

The χ^2 test of association was used to compare mesh and no-mesh groups with respect to percentages; the Mann-Whitney test was used to compare mesh and no-mesh groups with respect to noncategoric variables. Within each group, the McNemar test was performed to compare preoperative and postoperative percentages; the Friedman test was performed to compare preoperative and postoperative noncategoric variables.

[a] Patients who underwent reoperation for prolapse were excluded from the 12-month analyses; [b] Lower scores represent better outcome; [c] Higher scores represent better outcome; [d] Prolapse and Incontinence Sexual Questionnaire, item 5, response = usually or always.

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Board of Urology accredited fellowship programs.

To date, 3 RCTs have been conducted that have evaluated mesh for vaginal prolapse repair in the anterior compartment only. Hiltunen et al[4] reported a higher cure rate for anterior repair with polypropylene mesh overlay at 1 year, but with a 17% exposure rate. This is consistent the 15.6% mesh exposure rate that halted our trial.[12] The trial of Hiltunen et al excluded women with apical prolapse that required treatment or those with primarily posterior prolapse; our study included women with stage ≥2 prolapse in any compartment. The second RCT used blinded examiners, like our trial, and showed a cure rate of 55% for anterior repair vs 87% for Perigee (American Medical Systems, Minnetonka, MN) at 1 year.[5] One potential limitation of their study, however, was its support by an educational grant from the company that makes the mesh that was used in the trial.

Recently, Altman et al[20] randomly assigned 200 women to Prolift and 189 women to traditional colporrhaphy at 53 Nordic hospitals. Their trial found a significantly higher cure rate for the anterior compartment in the mesh group (60.8% vs 34.5%). Similar to our trial, they found more complications in the mesh group. Their trial had some important differences from ours. First, ours was a multicompartment mesh RCT; theirs was anterior only. Also, only a small percentage of their patients had clinically significant apical prolapse, whereas the median stage of apical prolapse in our trial was stage 2-3. Additionally, examiners in their trial were not masked to the treatment group.

Two trials evaluated mesh use for multicompartment defects. One trial found no difference between traditional colporrhaphy and polypropylene mesh overlay for combined anterior and posterior prolapse at 1 year.[21] However, women were excluded if prolapse was present only in the anterior or posterior compartment or if apical prolapse was present beyond the hymen. Our trial included women with stage ≥2 prolapse in any compartment. More recently, Withagen et al[22] performed a multicenter RCT at 13 sites that compared Prolift to conventional vagi-

TABLE 5
Reoperations for erosions and prolapse recurrence

Patient	Initial surgery	Indication for reoperation	Extrusion/exposure or recurrence site	Surgery	Reoperation time
1[a]	Total Prolift, partial vaginectomy of excess 14-cm vagina	Extrusion, 2 cm	Posterior	Excision of mesh	10 wk
		Prolapse	Stage 4 apical, anterior, posterior	Abdominal sacral colpopexy	9.8 mo
2	Total Prolift	Extrusion, 1 × 2 cm	Posterior	Excision of mesh	4 mo
3[b]	Anterior Prolift, transobturator sling	Persistent voiding dysfunction, prolapse	Stage 2 posterior, stage 1 apical, enterocele	Sling revision, iliococcygeal suspension	4.6 mo
4	Anterior Prolift	Prolapse	Stage 3 posterior, enterocele	Robotic sacral colpopexy	10 mo
5[c]	Anterior Prolift	Exposure, 5-mm; worsened stress urinary incontinence symptoms	Anterior	Excision of mesh, retropubic sling	10 mo

Prolift; Ethicon Women's Health and Urology, Somerville, NJ.

[a] Anterior recurrence was noted at 8 weeks, with stage 4 recurrence at 9.5 months; [b] Transobturator sling procedure was performed for stress urinary incontinence with preoperative diagnosis of detrusor hypoactivity and Valsalva voiding; prolapse recurrence that was noted intraoperatively was fixed at the time of sling release because of the belief that recurrent prolapse was contributing to voiding dysfunction; [c] Interval collagen was planned if mild preoperative stress urinary incontinence symptoms worsened; the patient had 1 week of improvement after collagen and sling procedure was then performed for definitive stress urinary incontinence cure.

Sokol. RCT of mesh for prolapse repair. Am J Obstet Gynecol 2012.

nal prolapse repair. Although their study showed higher cure rates in the treated compartment in the mesh group, examiners were unblinded. Despite unblinded examiners, they reported failure rates of 66% in the conventional group and 49% in the mesh group when failure was defined as overall pelvic organ prolapse as stage ≥2. As in our double-blind trial, these failure rates are higher than reported elsewhere in the literature. Moreover, they reported an exposure rate of 16.9% at 1 year, which is consistent with our exposure rate of 15.6%. In their trial, 22 different surgeons were involved, with some contributing as few as a single subject to the study. Although this may have resulted in higher failure and exposure rates in their trials, it may more closely represent "real world" experience, where some surgeons perform these repairs infrequently.

Our relatively low objective cure rate may be due to a number of factors. First, we used stringent objective outcome criteria. Despite our high objective "failure" rate, most participants were happy with their repair, had improved QOL, and were not symptomatic of recurrent prolapse. Indeed, >75% of objective recurrences occurred proximal to the hymen, and prolapse above the hymen is rarely symptomatic.[23,24] Second, investigators who were masked to the procedure performed postoperative examinations, which reduced the risk of surgeon bias. As we previously reported,[12] cure rates for synthetic mesh procedures have been reported to be as low as 43.7% for stage <2 when blinded examinations are performed.[25] One recent RCT that compared laparoscopic sacral colpopexy to total Prolift for prolapse after hysterectomy found a 77% cure rate at 2 years in the laparoscopy group vs 43% in the vaginal mesh group ($P = .006$).[26] Similar to our trial, examiners were blinded to treatment allocation, and cure rates for vaginal prolapse repair were lower than reported in non-RCTs. Third, we had excellent (92.3%) follow-up evaluations at 1 year. This is higher than many of the studies with >1-year follow up. Twenty-four to 40% loss to follow-up rates in these studies[9,27] may have changed their reported cure rates greatly. We do agree with Jacquetin et al[28] that shortcomings of the POP-Q may explain some of the anatomic "failures" after prolapse repair because the POP-Q cannot differentiate between distal anterior prolapse (ie, ureterocele) and more clinically relevant mid-vaginal prolapse. As stated by Barber et al,[29] "the definition of success substantially affects treatment success rates after pelvic organ prolapse surgery. The absence of vaginal bulge symptoms postoperatively has a significant relationship with a patient's assessment of overall improvement, although anatomic success alone does not."

Despite a significantly shorter follow-time in the mesh group, our study found a significantly higher reoperation rate in participants who received mesh. This is consistent with a systematic review by Diwadkar et al,[30] who reported that the total reoperation rate was highest with vaginal mesh kits compared with procedures that were performed vaginally and abdominally.[30]

High-quality RCTs are necessary to inform clinical decisions regarding mesh use in pelvic reconstructive surgery. A lack of high-quality evidence persists, despite the widespread use of vaginal mesh procedures. Clinical practice guidelines regarding mesh use that have been published by the Society of Gynecologic Surgeons could not make recommendations about the use of synthetic graft for multiple compartment disease because of a lack of comparative studies on which to base recommendations.[31]

Lighter meshes and trocar-less delivery systems likely will decrease complications that are associated with vaginal

mesh use. Nonetheless, properly designed clinical trials are necessary to evaluate whether synthetic mesh confers benefit for vaginal prolapse repair. Based on the results of this study and the high exposure rates that have been noted in other studies, risks may outweigh benefits for the older trocar-based mesh systems, even when fellowship-trained pelvic reconstructive surgeons perform these procedures. ■

REFERENCES

1. Olsen AL, Smith VJ, Bergstrom JO, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89:501-6.
2. Abdel-Fattah M, Ramsay I, on behalf of the West of Scotland Study Group. Retrospective multicentre study of the new minimally invasive mesh repair devices for pelvic organ prolapse. BJOG 2008;115:22-30.
3. Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (Prolift technique): a case series multicentric study. Int Urogynecol J 2007;18:743-52.
4. Hiltunen R, Nieminen K, Takala T, et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007;11:455-62.
5. Nguyen JN, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. Obstet Gynecol 2008;111:891-8.
6. Wetta LA, Gerten KA, Wheeler TL, Holley RL, Varner RE, Richter HE. Synthetic graft use in vaginal prolapse surgery: objective and subjective outcomes. Int Urogynecol J 2009;20:1307-12.
7. Altman D, Vayrynen T, Engh ME, Axelson S, Falconer C. Short-term outcome after transvaginal mesh repair or pelvic organ prolapse. Int Urogynecol J 2008;19;787-93.
8. Gauruder-Burmester A, Koutouzidou P, Rohne J, Gronewold M, Tunn R. Follow-up after polypropylene mesh repair of anterior and posterior compartments in patients with recurrent prolapse. Int Urogynecol J 2007;18:1059-64.
9. van Raalte HM, Lucente VR, Molden S, Haff R, Murphy M. One-year anatomic and quality-of-life outcomes after the Prolift procedure for treatment of posthysterectomy prolapse. Am J Obstet Gynecol 2008;199:694.e1-6.
10. Food and Drug Administration. Public health notification: serious complications associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence issued October 20, 2008. Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm. Accessed July 5, 2011.
11. Mucowski SJ, Jurnalov C, Phelps JY. Use of vaginal mesh in the face of recent FDA warnings and litigation. Am J Obstet Gynecol 2010;203:103.e1-4.
12. Iglesia CB, Sokol AI, Sokol ER, et al. Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol 2010;116:293-303.
13. Shull BL, Bachofen C, Coates KW, Kuehl TJ. A transvaginal approach to repair of apical and other associated sites of pelvic organ prolapse with uterosacral ligaments. Am J Obstet Gynecol 2000;183:1365-74.
14. Weber AM, Abrams P, Brubaker L, et al. The standardization of terminology for researchers in female pelvic floor disorders. Int Urogynecol J 2001;12:178-86.
15. Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33.
16. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol 2005;193:103-13.
17. Rogers R, Kammerer-Doak D, Villarreal A, Coates K, Qualls C. A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse. Am J Obstet Gynecol 2001;184:552-8.
18. Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003;189:98-101.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
20. Altman D, Väyrynen T, Engh ME, Axelsen S, Falconer C. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011;364:1826-36.
21. Carey M, Higgs P, Goh J, et al. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. BJOG 2009;116:1380-6.
22. Withagen MI, Milani AL, Boon J, Vervest HA, Vierhout ME. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. Obstet Gynecol 2011;117:242-50.
23. Swift S, Woodman P, O'Boyle A, et al. Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005;192:795-806.
24. Gutman RE, Ford DE, Quiroz LH, Shippey SH, Handa VL. Is there a pelvic organ prolapse threshold that predicts pelvic floor symptoms? Am J Obstet Gynecol 2008;199:683.e1-7.
25. Wetta LA, Gerten KA, Wheeler TL, Holley RL, Varner RE, Richter HE. Synthetic graft use in vaginal prolapse surgery: objective and subjective outcomes. Int Urogynecol J 2009;20:1307-12.
26. Maher CF, Feiner B, DeCuyer EM, Nichols CJ, Hickey KV, O'Rourke P. Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. Am J Obstet Gynecol 2011;204:360.e1-7.
27. Moore RD, Beyer RD, Jacoby K, Freedman SJ, McCammon KA, Gambia MT. Prospective multicenter trial assessing type I, polypropylene mesh placed via transobturator route for the treatment of anterior vaginal prolapse with 2-year follow-up. Int Urogynecol J 2010;21:545-52.
28. Jacquetin B, Fatton B, Rosenthal C, Clavé H, Debodinance P, Hinoul P, et al. Total vaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 3-year prospective follow-up study. Int Urogynecol J 2010;21:1455-62.
29. Barber MD, Brubaker L, Nygaard I, et al. Defining success after surgery for pelvic organ prolapse. Obstet Gynecol 2009;114:600-9.
30. Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and re-operation rates after apical vaginal prolapse surgical repair. Obstet Gynecol 2009;113:367-73.
31. Murphy M, for the Society of Gynecologic Surgeons Systematic Review Group. Clinical practice guidelines on vaginal graft use from the Society of Gynecologic Surgeons. Obstet Gynecol 2008;112:1123-30.